



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>6</sup> : <b>B05B 11/00, 5/025, 5/16</b>		A1	(11) International Publication Number: <b>WO 99/49984</b> (43) International Publication Date: 7 October 1999 (07.10.99)
(21) International Application Number: PCT/IB99/00474			(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 22 March 1999 (22.03.99)			
(30) Priority Data: 9806937.0 31 March 1998 (31.03.98) GB			
(71) Applicant (for all designated States except US): THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): RENNIE, Paul, John [GB/GB]; Ataraxia, Ballfield Road, Godalming, Surrey GU7 2HA (GB). WILKINSON, Eric [GB/GB]; 14 Chequers Croft, Hilton, Cambridge PE18 9PD (GB). PIETERS, Julian, Robert [GB/GB]; 22 Priory Road, Cambridge CB5 8HT (GB). LAWSON, Robert, Andrew [GB/GB]; 1 Clare Street, Cambridge CB4 3BY (GB).			
(74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217-1087 (US).			
(54) Title: NASAL SPRAY DEVICE WITH ELASTOMERIC VALVE			
(57) Abstract			
<p>The invention relates to a spray device adapted to provide multiple, unit doses of a fluid, each dose having a volume in the range from about 1 to about <math>100 \mu\lambda</math>, the device comprising an elastomeric, self-sealing valve having a fluid side and a delivery side, the valve opening to allow passage of the fluid when pressure is applied to fluid on the fluid side and sealing when the pressure is removed. The valve achieves a clean stop-start flow of the fluid at low fluid volumes. The device is particularly suitable for low volume medical applications such as nasal spraying.</p>			
<p><b>Published</b>  <i>With international search report.  Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>			

***FOR THE PURPOSES OF INFORMATION ONLY***

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

## NASAL SPRAY DEVICE WITH ELASTOMERIC VALVE

5

### Field of the Invention

The present invention relates to a spray device adapted to provide multiple, unit doses of a fluid, the device comprising an elastomeric, self-sealing valve which achieves a clean stop-start flow of the fluid at low fluid volumes. More particularly, the invention relates to a device delivering unit volumes in the range from about 1 to 10 10 about 100 µl.

### Background of the Invention

Treatment of maladies affecting the nasal region, such as hay fever or congestion due to colds, has long been effected by means of a nasal spray device. More recently it has been recognised that the mucous membranes of the nasal cavity can be used as a 15 convenient delivery site for drugs targeted at other areas of the body. See for example WO 92/11049 which discloses a pen shaped device for nasal administration of, particularly, insulin. A spray form is often convenient for such treatments. Treatment of the eyes can also conveniently be effected by a spray device. Preferred volume doses for such applications are generally low, down to less than 10 µl. 20 Typically, repeat dosing will be required in order to make a treatment fully effective. Achieving clean stop-start flow from spray devices delivering such low volumes can be difficult. Typical problems encountered include residual weeping from a valve after application, with the potential for back contamination, and valve clogging.

It has now been found that an elastomeric valve, particularly a slit valve, provides 25 clean stop-start flow without clogging, even if the sprayed fluid comprises a finely divided particulate solid.

Accordingly, it is an object of the present invention to provide a spray device which efficiently delivers multiple unit doses at low unit volume.

It is yet a further object of this invention to provide a spray cut-off device which 30 provides a clean cut-off of the spray and is not susceptible to clogging.

### Summary of the Invention

According to the present invention there is provided a spray device, adapted to provide one or more unit doses of a fluid, the or each dose having a volume in the

range from about 1 to about 100 µl, the device comprising an elastomeric, self-sealing valve having a fluid side and a delivery side, the valve opening to allow passage of the fluid when pressure is applied to fluid on the fluid side and sealing when the pressure is removed.

- 5 Preferably the spray device is an electrostatic spray device which charges the spray before entry into the nostrils.

#### Detailed Description of the Invention

##### Fluids

The spray device of the invention preferably comprises a fluid reservoir containing a pharmaceutically acceptable fluid, the fluid comprising a pharmaceutically acceptable treatment agent selected from medicaments, flavours, salts, surfactants and mixtures thereof. The fluid optionally comprises other adjuvants dissolved or dispersed within it. The fluid can be aqueous or non-aqueous. Suitable aqueous fluids include water and mixtures of water with water-miscible solvents such as glycerol, propylene glycol, or alcohols such as ethanol or isopropyl alcohol. Aqueous emulsions can also be used, either water-in-oil or oil-in water emulsions. Preferably the fluid is an aqueous solution, dispersion or oil-in-water emulsion. Suitable non-aqueous fluids comprise polyethylene glycols, glycerol, propylene glycol, dimethyl isosorbide, silicone oils, ketones, ethers and mixtures thereof.

20 Although not limited to any particular range of resistivity, the invention has particular application to low resistivity fluids, especially those having a bulk resistivity of less than  $1 \times 10^8$  ohm.cm, preferably those having a resistivity of less than  $1 \times 10^4$  ohm.cm, more preferably less than  $1 \times 10^3$  ohm.cm. If necessary, the fluid may comprise a resistivity modifier, such as a pharmaceutically acceptable salt, in order to bring the bulk resistivity within the required range.

25 The fluid is preferably a pharmaceutically acceptable intranasal carrier. Preferably, the nasal composition is isotonic, i.e., it has the same osmotic pressure as blood and lacrimal fluid. The desired isotonicity of the compositions of this invention may be accomplished using, for example, the sodium chloride already present, or other pharmaceutically-acceptable agents such as dextrose, boric acid, citric acid, sodium tartrate, sodium citrate, sodium phosphate, potassium phosphate, propylene glycol or other inorganic or organic solutes. Sodium chloride is preferred particularly for buffers containing sodium ions. Further examples of sodium chloride equivalents are

disclosed in Remington's Pharmaceutical Sciences pp. 1491-1497 (Alfonso Gennaro 18th ed. 1990), which is herein incorporated by reference.

#### Medicaments

The fluid can comprise a wide range of medicaments. By "medicament" is meant a drug or other substance intended to have a therapeutic effect on the body. Suitable levels of the medicament are from 0.001 to 20%, preferably from 0.01 to 5%, more preferably from 0.1 to 5%. It will be appreciated that the levels of specific medicaments will depend on many factors including their potency, safety profile, solubility / ease of dispersion and intended effect. The medicament, when used, can be one which is intended to have an effect at the site of application, such as a decongestant, antihistamine or anti-inflammatory drug, or it may be intended for systemic absorption such as an anti-viral, anti-depressant, anti-emetic, anti-pyretic medicament or a hormone or such-like. The medicament can be soluble in the fluid or can be an insoluble, finely divided particulate liquid or solid dispersed within the fluid.

Suitable decongestants include oxymetazoline, tramazoline, xylometazoline, naphazoline, tetrahydrazoline, pseudoephedrine, ephedrine, phenylephrine, their pharmaceutically acceptable salts, such as the hydrochlorides, and mixtures thereof. Preferred decongestants are selected from oxymetazoline, xylometazoline, their pharmaceutically acceptable salts and mixtures thereof. Especially preferred for use herein is oxymetazoline hydrochloride which is soluble in water. When used in the compositions of the present invention, the decongestant is preferably present at a concentration of from about 0.01% to about 3.0%, more preferably from about 0.01% to about 1%.

Antihistamines useful to the present invention include, but are not limited to, fast-acting, histamine H-1 receptor antagonists. Such H-1 receptor antihistamines may be selected from among the following groups of antihistamines: alkylamines, ethanolamines, ethylenediamines, piperazines, phenothiazines, piperidines. Examples of useful fast acting antihistamines include acrivastine, carboxamine, diphenhydramine, chlorpheniramine, brompheniramine, dexchlorpheniramine, doxylamine, clemastine, promethazine, trimeprazine, methdilazine, hydroxyzine, pyrilamine, tripeleannamine, meclizine, triprolidine, azatadine, cyproheptadine, rocastine, phenindamine or pharmaceutically acceptable salts and mixtures thereof. Other useful antihistamines include terfenadine, azelastine, cetirizine, astemizole, ebastine,

ketotifen, Iodoxamide, loratadine, levocabastine, mequitazine, oxatomide, setastine, tazifylline, temelastine or pharmaceutically acceptable salts and mixtures thereof. When used in the compositions of the present invention, the antihistamine component is preferably present at a concentration of from about 0.01% to about 3.0%, more preferably from about 0.01% to about 1%.

The medicament can also be an anti-inflammatory agent such as a corticosteroid. Particularly preferred agents within this class are glucocorticoids selected from the group consisting of beclomethasone, flunisolide, fluticasone, memetasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. When used in the compositions of the present invention, the anti-inflammatory agent is preferably present at a concentration of from about 0.001% to about 0.1%, more preferably from about 0.01% to about 0.1%.

Also useful herein are xanthine derivatives such as caffeine and methylxanthine and the like; antiallergics; mucolytics; anticholinergics; non-opiate analgesics such as acetaminophen, acetylsalicylic acid, ibuprofen, etodolac, fenuprofen, fenoprofen, ketorolac, flurbiprofen, indomethacin, ketoprofen, naproxen, pharmaceutically acceptable salts thereof and mixtures thereof; opiate analgesics such as butorphanol; leukotriene receptor antagonists; mast cell stabilisers such as cromolyn sodium, nedocromil and Iodoxamide; and lipoxygenase inhibiting compounds.

Further examples of suitable medicaments can be found in WO97/46243, EP-A-780127, US-A-5,124,315, US-A-5,622,724, US-A-5,656,255 and US-A-5,705,490

#### Flavours

Various flavouring and/or aromatic components (e.g., aldehydes and esters) can be used in the fluids of the invention. These include, for example, menthol, camphor, eucalyptol, benzaldehyde (cherry, almond); citral (lemon, lime); neral; decanal (orange, lemon); aldehyde C-8, aldehyde C-9 and aldehyde C-12 (citrus fruits); tolyl aldehyde (cherry, almond); 2,6-dimethyl-octanal (green fruit); 2-dodecenal (citrus, mandarin); and herbal components such as thyme, rosemary and sage oils. Additional aromatic components suitable for use in the present invention include those described in U.S. Patent 4,136,163 to Watson et al., U.S. Patent 4,459,425 to Amano et al., and U.S. Patent 4,230,688 to Rowsell et al.; all of which are herein incorporated by reference. Mixtures of these aromatics can also be used.

Surfactants

The fluid can also comprise one or more pharmaceutically acceptable surfactants. Such surfactants can be useful for dispersing or emulsifying medicaments or flavours, for enhancing absorption across the nasal membrane or as treatment agents in their own right, such as for softening earwax. The surfactants can be anionic, nonionic, cationic or amphoteric, preferably they are nonionic. Typical nonionic surfactants useful herein include: polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as polysorbate 80; polyoxyethylene derivatives of fatty acids such as polyoxyethylene 50 stearate, as well as oxyethylated tertiary octyl phenol formaldehyde polymer (available from Sterling Organics as Tyloxapol) or mixtures thereof. The usual concentration is from 0.1% to 3% by weight.

Salts

The fluid can also comprise one or more pharmaceutically acceptable salts. The salt can mineral salts such as e.g. sodium chloride, or salts of organic acids such as sodium citrate.

Other adjuvants

The fluid can further comprise other ingredients such as thickeners, humectants, suspending aids, encapsulating aids, chelating agents and preservatives.

The viscosity of the compositions may be maintained at a selected level using a pharmaceutically-acceptable thickening agent. Suitable thickening agents include, for example, xanthan gum, methyl cellulose, microcrystalline cellulose, carboxymethyl cellulose, chitosan, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose, carboxyvinyl polymer, carbomer, and the like or pharmaceutically acceptable salts thereof. Mixtures of such thickening agents may also be used. The preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the selected viscosity. Viscous compositions are normally prepared from solutions by the addition of such thickening agents.

Fluids useful in the present invention can also comprise from about 0.01% to about 30 5% of a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of pharmaceutically-acceptable humectants can be employed including, for example sorbitol, propylene glycol, polyethylene glycol, glycerol or mixtures thereof. As with the thickeners, the concentration will vary with

the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

A pharmaceutically-acceptable preservative is generally employed to increase the shelf life of the compositions of the present invention. A variety of preservatives including, for example, benzyl alcohol, parabens, phenylethyl alcohol, thimerosal, chlorobutanol, chlorhexidine gluconate, or benzalkonium chloride can be employed. The most preferred preservative system for use herein comprises a combination of benzalkonium chloride, chlorhexidine gluconate and disodium EDTA as a chelating agent. A suitable concentration of the preservative will be from 0.001% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected.

#### Spray devices and spray characteristics

The spray device will generally comprise a means for controlling the dosage of the dispensed fluid. This can be as simple as an on-off switch which allows the user to control the dosage according to his or her needs. The spray device is adapted to provide one or more unit fluid doses, preferably multiple fluid doses, each with a volume in the range of from about 1 to about 100 µl, preferably from about 1 to about 20, more preferably from about 5 to about 15 µl. The dose volume is preferably pre-set but it can also be adjusted by the user to a desired volume. The device suitably comprises a reservoir for holding the fluid and a dosing means for selectively delivering a unit dose from the reservoir to the spray generator. The dosing means can be, for example, a metered valve or a syringe pump.

The device is preferably adapted to produce a spray having a fluid ligament, the ligament extending from the nosepiece and having a nosepiece end and a delivery end, the spray further comprising a spray cone diverging from the delivery end of the ligament. By "nosepiece end" is meant the point at which a plane (hereinafter the nosepiece plane) drawn perpendicular to the axis of the ligament and just touching the exterior of the nosepiece would intersect the centre of the ligament. The ligament preferably has a length of from about 1 to about 20 mm, more preferably from about 1 to about 10 mm, yet more preferably from about 2 to about 8 mm, and especially from about 3 to about 6mm from the nosepiece end to the delivery end.

In preferred embodiments the spray cone has a cone angle of from about 10 to about 90°, preferably 20 to about 50°, more preferably from about 30 to about 40°. In electrostatic devices, the length of the ligament and the spray cone angle can be

adjusted by varying the viscosity or surface tension of the fluid, by varying the fluid flow rate or exit velocity, or by varying the electrical field strength through applied voltage, potential gradient or by use of a field intensifying electrode.

The total length of the ligament can be, and preferably is, longer than the length from the nosepiece end to the delivery end since the ligament preferably originates from a point on the device side of the nosepiece plane, such as from an elastomeric, self-sealing valve as disclosed herein, and passes through a passage in the nosepiece. Suitably the distance from the point of origin of the ligament to the nosepiece plane is in the range from about 2 mm to about 15 mm, preferably from about 3 to about 10 mm and more preferably from about 5 to about 9 mm. In this way the nosepiece can be employed as a field intensifier which helps to control the ligament length. For this purpose the nosepiece is preferably a non-conducting material such as a plastic which can be e.g. polypropylene but is preferably a soft thermoplastic elastomer which provides for greater comfort if held against the nose. Elastomers described herein for the self-sealing valve are also suitable for the nosepiece.

Electrostatic devices suitable for ligament mode spraying are described in WO 96/40441, in EP-A-501,725 and in co-pending application PCT/GB97/02746. Preferably the present device is a device according to embodiments of EP-A-501,725 or PCT/GB97/02746 in which a jet is created by mechanical means and an applied high voltage leads to the jet or ligament breaking up into a spray cone. The jet can be generated by, for example, a syringe pump. Suitable jet velocities are from about 0.5 to about 8, preferably from about 1 to about  $3 \text{ ms}^{-1}$ .

A suitable high voltage is in the range from about 1 kV up to about 15 kV, preferably from about 2kV to about 10kV and more preferably from about 2kV to about 5kV. The voltage can conveniently be applied, even within the constraints of a small hand-held device, from a low voltage (1.5V is sufficient) battery coupled to a step-up transformer. The battery is preferably of the long-life type and can be rechargeable. If a metal syringe pump is used, the voltage can be applied to the fluid through the pump which is preferably encased in an insulating plastic housing. Alternatively, the fluid can be charged by an electrode inserted into the fluid. The generator can be activated by the user by means of an external switch which can also be used to mechanically prime the pump. Preferably the switch includes a metal portion by means of which the user completes an earth return path to the high voltage circuit. A suitable arrangement for the overall device construction is described in PCT/GB97/02746. In this way the user does not acquire a net charge. Alternate

arrangements, whereby an alternating voltage is applied, can also be used to prevent charge build-up.

- The device is activated to deliver the spray. The ligament of the spray extends through the nostril opening, into the vestibule and preferably to within a short distance of the nasal valve opening, before breaking up to form the spray cone. The device can be constructed simultaneously to dispense two sprays, directed to each of two nostrils. The two sprays can be generated from two separate dosing means or can be provided from a single source such as by using a 'Y' shaped valve to split a single jet into two.
- 10 In order to provide clean cut-off at low unit volumes the device comprises an elastomeric, self-sealing exit valve having a fluid side and a delivery side, the valve opening to allow passage of the fluid when pressure is applied to fluid on the fluid side and sealing when the pressure is removed. By "exit valve" is meant that the elastomeric valve is the final dispensing valve and that there are no other elements of 15 the device which mechanically, restrict or modify the flow of the fluid on the downstream side of the valve. In highly preferred embodiments herein the valve is a slit valve. The valve can comprise a single slit or two or more intersecting slits, to form a cross shape for example. Preferably, however, the valve comprises a single slit. Although the valve can be flat it is preferably dome-shaped by which is meant a 20 non-planar valve having a recess such as with a hemispherical or frustoconical dome. In preferred embodiments the valve is essentially in the form of a hemispherical dome having a flange along its perimeter so that a collar can be fitted to retain the valve in the device. The diameter of the valve, including the flange, is typically from about 2 to about 6 mm with the dome portion having a diameter of from about 1 to about 4 25 mm, typically about 2.5mm and a thickness from inside to out of from about 0.5 to about 1.5 mm, suitably about 1 mm. The valve need not be of uniform thickness. In preferred embodiments the valve dome's exterior surface is hemispherical whereas the internal surface is formed with a small flat at the top of the dome where the slit is formed. Suitable slit widths are from about 50 to about 400  $\mu\text{m}$ , preferably from 30 about 150 to about 250  $\mu\text{m}$ . It is to be understood that the slit width refers to the longest dimension of the slit when first created. The term "elastomer" herein refers to a material which is both elastically compressible and elastically extensible. A wide range of elastomers can be used, including but not limited to polyurethanes; chloroprene, butyl, butadiene and styrene-butadiene rubbers, and silicone elastomers 35 such as 2 part room temperature vulcanising (RTV) silicones. Preferred for use

herein are the 2 part silicone RTVs. Suitable silicone RTVs are available under the trademark NuSil and have a hardness of from about 30 to about 80 Shore A, preferably from about 40 to about 70 Shore A. The elastomers can optionally be mixed with a suitable plasticiser or foaming agent to make them more compressible.

- 5      The elastomer may also have other materials dispersed within it in order to modify the its properties, such as its conductivity. If elastomers of low tear strength are employed, the slit width may grow if the slit is held open for a prolonged period of time. The slit valve can be formed by piercing an injection moulded elastomeric seal, of the same dimensions and shape as the intended valve, with a pin having a  
10     sharpened tip. The slit width is roughly proportional to the pin width. The pin can be a flat blade or can have a polygonal or round cross-section. The pin preferably has a polygonal or, especially, a round cross-section. It has been found that sharp-edged pins create a cut which behaves in use as a flap rather than a hole. This can lead to a jet which is not straight or even to the creation of two or more jets which may lead to  
15     unreliable or unpredictable spraying. Suitable pin diameters are from about 100 to 350, more preferably from 150 to 250  $\mu\text{m}$  in diameter. When silicone elastomers are used it is preferred that the piercing pin is withdrawn rapidly after forming the slit to avoid undesired slit growth. It has further been found that the geometry of the  
20     elastomeric seal and the method of piercing have a significant effect on the effectiveness and reproducibility of slit formation. More reliable slit formation is obtained if the seal is pierced from the inside of the dome rather than from the outside.

- The valve opens when pressure is applied to fluid on the fluid side and seals when the pressure is removed. As mentioned earlier, pressure can be applied to the fluid by of  
25     a dosing means such as a syringe pump. The applied pressure is suitably in the range from about 200 to about 5000 mbar (20 to 500 kPa), preferably from about 500 to about 3000 mbar (50 to 300 kPa). The flow rate through the valve is generally proportional to the pressure applied and is suitably in the range from about 5 to about 50, more preferably from about 5 to about 30  $\mu\text{l s}^{-1}$ . At such pressures and with the  
30     disclosed valve type and slit dimensions a straight fluid ligament with an exit velocity of from about 0.5 to about 8 preferably from about 1 to about 3  $\text{m s}^{-1}$  is obtained.

- The diameter of the issuing ligament is partly determined by the flow rate and is generally less than the width of the slit valve. Depending on the flow rate, ligament diameters of less than 50  $\mu\text{m}$  can be achieved, even when a valve slit width of 200  $\mu\text{m}$  is employed. The ligament diameter strongly influences the particle size of the  
35

spray after break-up into the spray cone, the particle size being broadly similar to the ligament diameter. It is a feature of the ligament mode electrostatic spraying herein that a tightly distributed, almost mono-disperse spray is obtained. It is thus possible to achieve a spray with a median droplet size of from 20 to about 80, preferably from 5 about 30 to about 70  $\mu\text{m}$ , more preferably from about 40 to about 60  $\mu\text{m}$ , the particle size distribution generally having a standard deviation of less than 5, typically less than 2  $\mu\text{m}$ , and preferably less than 1  $\mu\text{m}$ . It is commonly understood that, for nasal spraying, a particle size of 10  $\mu\text{m}$  or less is desirable so that the particles are not carried through into the lungs. It is believed, however, that having an electrostatic 10 charge on the spray particles makes them much less likely to be carried beyond the nose since the charged particles tend to find an earthed surface rather quickly.

The clean stop performance of the tip valve can be further improved by introducing a pressure relief feature behind the valve. This would take the form of a by-pass to the fluid reservoir so that any residual fluid pressurised by relaxation of the elastomer 15 would return to a reservoir rather than dripping from the valve exit.

If necessary, several self-sealing valves can be used in tandem to achieve higher volume throughputs whilst retaining the advantageously small spray particle sizes. The seals from which the valves are made can conveniently be manufactured by a conventional injection moulding process.

## 20 Methods

The spray device herein is suitable for spraying into a bodily cavity, particularly into the nose, mouth or ears of a human. The low volume and gentle spray also make it suitable for e.g. ophthalmic spraying. Preferably the device is a nasal spray device. A preferred method of administering a fluid to the nasal cavity from the spray device 25 comprises spraying the fluid into the nasal cavity without substantial penetration of the device into the nostrils. By "without substantial penetration into the nostrils" herein is meant that there is no insertion of a nozzle or such-like into the nasal vestibule. In use, the nosepiece of the device is preferably placed in contact with the nostril opening to obtain the full benefit of the field intensifying effect described 30 herein in relation to the nosepiece. If pressure is applied by the user, for certainty of contact or to assist in orientation there may be some flaring of the nostril or overlap with the septum cartilage but nevertheless the nosepiece will not be completely surrounded by the nostril.

The invention will now be described by way of example only, with reference to the accompanying drawings in which:

- Fig. 1 is a sectional view through a human nose.
- Fig. 2 is a perspective view of a spray device according to the invention.
- 5 Fig. 3 is a greatly simplified sectional view of the spray device of Figure 2 showing the relationship of the elastomeric nozzle to the nosepiece and dosing means.
- Fig. 4 is a schematic part section showing a spray issuing from a device according to the invention.
- Fig. 5 is an enlarged sectional view of an elastomeric exit valve according to the  
10 invention.

Referring to Fig. 1, the nose comprises a nasal cavity 1 in which are located the turbinates 2, convoluted finger-like structures covered with epithelium and which are susceptible to inflammation. The exterior opening to the nasal cavity is through two nostrils 3. Since the turbinates are located in the posterior part of the nasal cavity it  
15 has generally been difficult to spray them effectively without inserting a spray device into the nostrils.

Referring to Figures 2 and 3, there is shown a spray device 4 fitted with a soft elastomeric nosepiece 5 which is designed to fit against a user's nostril opening without being inserted into the nostril. The nosepiece is provided with a passage 6 which connects to a syringe pump 7, the interior detail of which is not shown, which is used to generate the ligament of the spray through elastomeric exit valve 8. The insulating casing 9 of the device further encloses (not shown) a replaceable fluid reservoir, battery, transformer and electronic circuitry for supplying a high voltage from the transformer to the fluid. The device is supplied with an actuating mechanism 10 which mechanically primes the pump and triggers its release to deliver  
25 a pre-set unit dose of the fluid. The actuating mechanism includes a metal portion to provide an earth return from the user to the high voltage circuitry.

Referring now to Figure 4, a spray comprises ligament 11 and spray cone 12 having a cone angle  $\theta$ . In practice the cone angle can be measured by spraying from a fixed distance onto disclosing paper and then measuring the diameter of the spray pattern or by direct viewing of the spray using high speed video photography with back lighting. The ligament has a delivery end 13 where the ligament breaks up into the spray cone and a nosepiece end 14 defined as the point where plane A-A intersects

ligament 11. Plane A-A is drawn perpendicular to the axis of the ligament, just touching the tip of nosepiece 5.

Figure 5 illustrates an elastomeric exit valve 8 according to the invention. The nozzle, which is circularly symmetrical, comprises a flange 15 for securing the nozzle 5 to the spray device, a domed head 16, a recess 17 and a slit 18 extending from the recess to the top of the dome. The nozzle is formed by injection moulding a seal of essentially the same construction and then piercing the dome with a sharpened pin, of round cross-section and 200 µm diameter, from the inside of the recess.

#### Examples

10 The following examples further describe and demonstrate embodiments within the scope of the present invention. The examples are given solely for the purpose of illustration and are not to be construed as limitations of the present invention.

#### Example I

A fluid of the present invention is prepared by combining the following components 15 utilising conventional mixing techniques similar to that described below.

	Component	Wt %
	oxymetazoline hydrochloride	0.31
	sodium citrate dihydrate	1.75
	citric acid	0.35
20	Tyloxapol	0.70
	chlorhexidine digluconate	0.054
	benzalkonium chloride	0.02
	camphor	0.04
	eucalyptol	0.02
25	disodium EDTA dihydrate	0.01
	distilled water	q.s. 100ml

In an appropriately sized vessel, the above listed ingredients are added one at a time to water with mixing, allowing each to dissolve before adding the next. After all the ingredients have been added, purified water is used to bring the batch to the appropriate weight. The solution has a bulk resistivity of 120 ohm.cm. The solution 30

is charged into a flexible laminate reservoir and fitted into an electrostatic spray device of the kind indicated in figure 2. The device further comprises an elastomeric valve as shown in Fig. 5, the valve being held in place by a screw collar clamping the flange. The nosepiece of the device is held against the nostril and the device directed 5 such that the spray ligament will enter the nostril. On actuation of the device, the syringe pump builds pressure behind the valve to about 100 kPa (1000 mbar), opening the slit valve to a width of about 50 µm and dispensing 8 µl of the solution over a period of about 1 second. When the fluid is dispensed the valve closes 10 completely, preventing further fluid egress and contamination of the fluid in the reservoir. The dispensed fluid provides relief from nasal decongestion without causing noticeable wetness either on or inside the nose. The low dose volume and gentle delivery have the result that the user does not sense any appreciable physical impact from the spray.

Example II

- 15 A further fluid is prepared by combining the following components utilising conventional mixing techniques similar to that described in Example I.

	<b>Component</b>	<b>Wgt %</b>
	flunisolide	0.025
	chlorpheniramine	0.350
20	levocabastine	0.0125
	propylene glycol	2.000
	polyethylene glycol	1.000
	ethylenediamine tetraacetic acid	0.050
	benzalkonium chloride	0.010
25	distilled water	q.s. 100ml

Intranasal spray administration, in the manner of Example I, of approximately 10 µl of the fluid composition is used to provide relief from allergy or allergy-like symptoms.

Example III

- 30 A fluid of the present invention is prepared by combining the following components utilising conventional mixing techniques similar to that described in Example I.

<b>Component</b>	<b>Wt %</b>
beclomethasone dipropionate, monohydrate	0.042
chlorpheniramine	0.500
Avicel RC - 591 <sup>1</sup>	0.200
5 dextrose	5.100
polysorbate 80	0.050
benzalkonium chloride	0.020
phenylethyl alcohol	0.025
distilled water	q.s. 100ml

10 <sup>1</sup>microcrystalline cellulose and sodium carboxymethyl cellulose, supplied FMC Corporation.

Intranasal spray administration, in the manner of Example I, of approximately 10 µl of the fluid composition is used to provide relief from allergy or allergy-like symptoms.

**WHAT IS CLAIMED IS:**

1. A spray device, adapted to provide one or more unit doses of a fluid, the or each dose having a volume in the range from about 1 to about 100 µl, the device comprising an elastomeric, self-sealing exit valve having a fluid side and a delivery side, the valve opening to allow passage of the fluid when pressure is applied to fluid on the fluid side and sealing when the pressure is removed.  
5
2. A spray device according to Claim 1 which is adapted to provide multiple unit doses of a fluid.
3. A spray device according to Claim 1 or Claim 2 wherein the valve is a slit valve, the slit having a width of from 50 to 400 µm, preferably from 150 to 250 µm.  
10
4. A spray device according to any of Claims 1 to 3 wherein the valve is dome-shaped.
5. A spray device according to Claim 3 or Claim 4 wherein the slit has been formed with a sharpened round pin.  
15
6. An electrostatic spray device according to any of Claims 1 to 5.
7. An electrostatic spray device according to Claim 6 wherein the device is adapted to apply a voltage in the range of from 1 kV to 10 kV to the fluid.
8. A spray device according to any of Claims 1 to 7 wherein the device is adapted to apply a pressure in the range of from 200 to 5000 mbar (20 to 500 kPa) to the  
20 fluid.

1 / 3

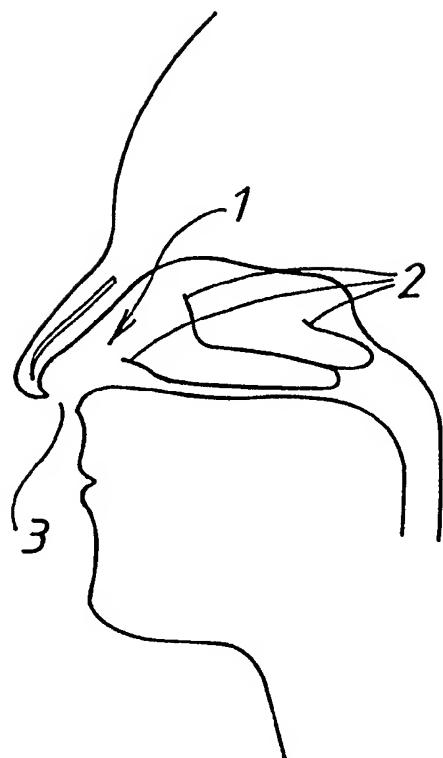


FIG. 1

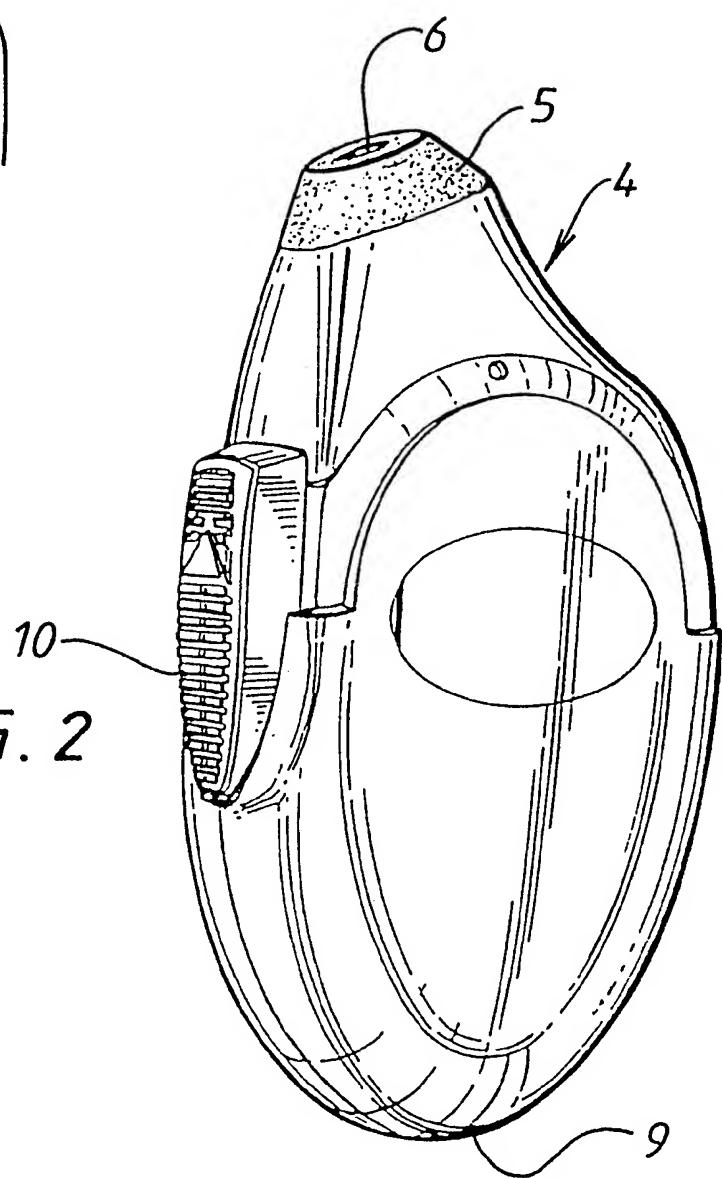


FIG. 2

2 / 3

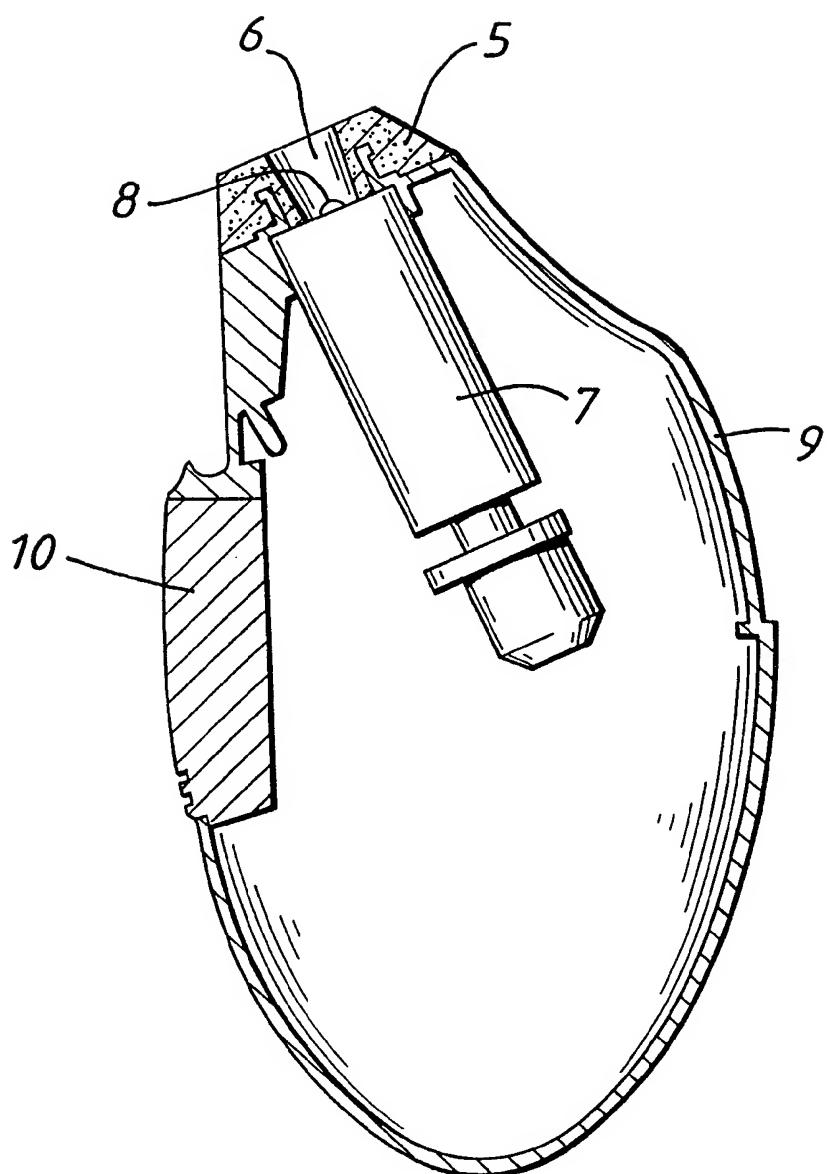


FIG. 3

3 / 3

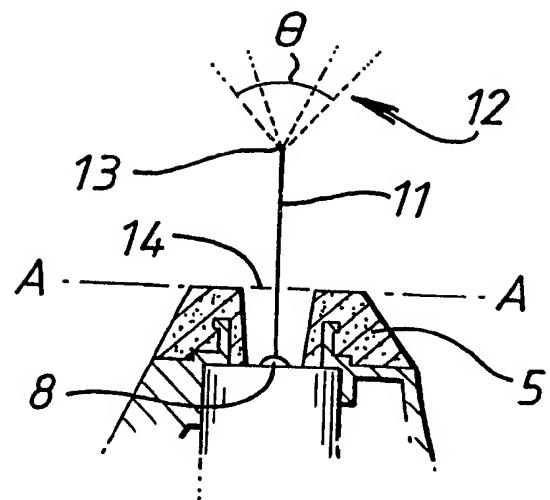


FIG. 4

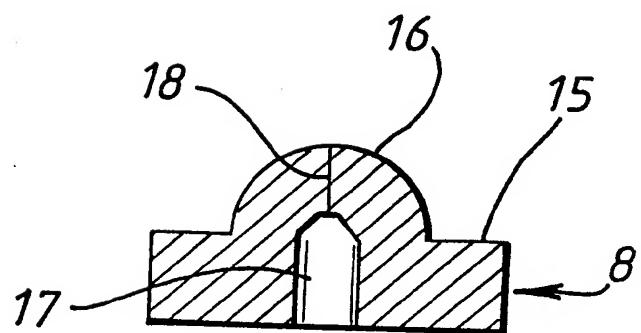


FIG. 5

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/IB 99/00474

**A. CLASSIFICATION OF SUBJECT MATTER**  
 IPC 6 B05B11/00 B05B5/025 B05B5/16

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
 IPC 6 B05B A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 511 538 A (SMEDLEY WILLIAM H ET AL) 30 April 1996 (1996-04-30) column 4, line 19 – line 48; figure 1 ---	1-4
A	EP 0 501 725 A (ICI PLC) 2 September 1992 (1992-09-02) cited in the application column 4, line 17 – line 56 column 6, line 43 – line 54 column 7, line 24 – column 8, line 1 column 16, line 30 – line 48 claims 2,3,7,19; figures 1,4 ---	1-4,6-8
A	GB 2 273 872 A (UNILEVER PLC) 6 July 1994 (1994-07-06) page 21, line 8 – page 23, line 2 figure 1 ---	3,6,7 --/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

20 July 1999

30/07/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Lakkis, A

**INTERNATIONAL SEARCH REPORT**

International Application No

PCT/IB 99/00474

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 98 30334 A (PROCTER & GAMBLE) 16 July 1998 (1998-07-16) abstract; figure 6 page 3, line 26 - line 36 page 7, line 14 - line 18 page 7, line 34 - line 37 -----	1-4

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 99/00474

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 5511538	A	30-04-1996	NONE		
EP 0501725	A	02-09-1992	AU	658859 B	04-05-1995
			AU	1124692 A	03-09-1992
			AU	671054 B	08-08-1996
			AU	2053895 A	10-08-1995
			CA	2062064 A	02-09-1992
			JP	5104035 A	27-04-1993
			US	5490633 A	13-02-1996
			US	5292067 A	08-03-1994
			ZA	9202475 A	15-04-1993
GB 2273872	A	06-07-1994	NONE		
WO 9830334	A	16-07-1998	US	5890655 A	06-04-1999
			AU	5715998 A	03-08-1998